NEUROPATHY VASCULITIC
A CLINICAL, PATHOLOGIC, AND ELECTROPHYSIOLOGIC CO-RELATIVE STUDY

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CERTIFICATE

This is to certify that the dissertation titled "Vasculitic Neuropathy A Clinical, Pathologic and Electrophysiologic Co-relative study" is the bonafide work of Dr. Arumugam Elango Eswaran in partial fulfillment of the requirements for D.M., Branch I (Neurology) examination of **THE TAMILNADU Dr M.G.R. MEDICAL UNIVERSITY** to be held in August 2009. The period of study was from January 2007 - December 2008.

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DECLARATION

I Dr. Arumugam Elango Eswaran , solemnly declare that the dissertation titled "Vasculitic Neuropathy A Clinical, Pathologic and Electrophysiologic Co-relative study" is the bonafide workdone by me at Govt. Stanley Medical College & Hospital from January 2007- December 2008 under the guidance and supervision of my PROF.A.MURUGESAN M.D., D.M., Professor and Head of the Department of Neurology.

This dissertation is submitted to the The Tamilnadu Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of D.M. Degree Branch – I Neurology.

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CONTENTS

INTRODUCTION

Peripheral nerve vasculitis is an important condition which can be diagnostically challenging and is one of the principal current indications for nerve and muscle biopsy. Previous studies have suggested that combined nerve and muscle biopsy produces a higher diagnostic yield than nerve biopsy alone in the investigation of vasculitis.

Peripheral nerve vasculitis is a pathological process involving infiltration of and injury to the walls of the vasa nervorum by inflammatory cells, [1-2] resulting in secondary ischaemia and damage to the nerve trunk. The diagnosis is difficult to make on clinical grounds alone and usually requires the biopsy of affected tissue prior to starting treatment. Although peripheral nerve vasculitis is rare, it remains one of the most important indications for performing a nerve biopsy.

Peripheral nerve vasculitis can occur either as part of multisystem disorders such as polyarteritis nodosa or connective tissue disorders (termed SVN, systemic vasculitic neuropathy)[1 3–5] or as a disorder restricted to the peripheral nervous system (termed NSVN, non-systemic vasculitic neuropathy).[6–8]

In both groups, striated muscle as well as peripheral nerve may show pathological signs of vasculitis. In 1988, Said and Lacroix reported that up to 45% of patients with

peripheral nerve vasculitis had demonstrable evidence of vasculitis in the peroneus brevis muscle (PBM) but not in the superficial peroneal nerve (SPN) when both were biopsied.[4] This group therefore suggested that combined SPN/ PBM biopsy (through a common incision) in patients with suspected peripheral nerve vasculitis would increase the diagnostic yield, an approach supported by more recent studies.[1 9]

Based on these studies it has also become accepted practice in units where the sural nerve is the more usual nerve biopsied to biopsy the vastus lateralis muscle as well (using a second incision during the same procedure) when vasculitis is being considered.

In order to determine whether combined nerve (usually sural) and vastus lateralis muscle biopsy improved diagnostic yield compared with nerve biopsy alone, I studied 30 cases of pathologically confirmed peripheral nerve vasculitis seen at our institution over a 2 year period.

REVIEW OF LITERATURE

Systemic vasculitis has been classically categorized as a primary disorder, such as polyarteritis nodosa, Churg-Strauss syndrome, and Wegener granulomatous, or as a secondary process, representing a complication from a connective tissue disorder (eg, rheumatoid vasculitis), infection, medication, or malignancy. Peripheral neuropathy is a well-recognized consequence of systemic vasculitis due to peripheral nerve infarction with Wallerian degeneration. Rarely, neuropathy is the sole manifestation of vasculitis, referred to as nonsystemic vasculitic neuropathy (NSVN). These conditions are defined pathologically by tissue biopsy demonstrating disruption or destruction of the vessel wall with inflammatory cell infiltrates. The diagnosis of vasculitic neuropathy is straightforward in patients with an established diagnosis of systemic vasculitis and classic features of mononeuritis multiplex. Most patients have clinical features of a subacute, progressive, generalised but asymmetric, painful, sensorimotor polyneuropathy. Laboratory tests often indicate features of systemic inflammation, such as an elevated sedimentation rate or positive anti-neutrophil cytoplasmic antibody, and electrodiagnostic evaluation shows multiple mononeuropathies or a confluent, asymmetric axonal neuropathy. Nerve and muscle biopsy is necessary to establish the diagnosis in most cases.

Nerve Biopsy

Over the years careful studies have lead to a consensus regarding the usefulness of biopsy for the diagnosis of vasculitis with peripheral nerve involvement. It seems that: 1) Only a percentage of diagnosed patients have a positive nerve biopsy 2) Combined Nerve and muscle biopsy adds to the overall diagnostic yield than either alone 3) The absence of a positive tissue biopsy does not exclude the disorder 4) Biopsy of "symptomatic sites"seems to improve the diagnostic yield. 5) Electromyography (EMG) and Nerve Conduction Studies (NCS) help in the selection of the biopsy site and 6) whole nerve biopsy more useful than fascicular biopsy.

Electrophysiological studies

The findings of NCS and EMG in the vasculidities with peripheral nerve involvement reflect its pathology. The findings are those of an axonal neuropathy involving both motor and sensory nerves at all levels. Studies are very useful demonstrating a "Mononeuritis multiplex" pattern and also a multi-fascic temporal involvement of the peripheral nerve lesions. Conduction block can be seen from nerve ischemia. Asymmetries in the compound action potential of different nerves can also substantiate a mononeuritic axonal pattern.

Causes of vasculitic neuropathy can be classified on the basis of size of the vessels or primary versus secondary vasculitis. A simple classification is based on

systemic vasculitis, causing vasculitic neuropathy with other constitutional symptoms or serologic abnormalities, versus nonsystemic vasculitis, which presents as neuropathy only.

Systemic vasculitis

Systemic necrotizing vasculitis: These vasculitides classically involve small and medium-sized arteries affecting multiple organ systems, including the peripheral and central nervous systems. Polyarteritis nodosa is the most common necrotizing vasculitis, with greater than 50% involvement of peripheral nerves. The necrotizing vasculitides include the following:

Polyarteritis nodosa

Churg-Strauss syndrome

Wegener granulomatosis

Overlap syndrome

Cryoglobulinemia

Hypersensitivity vasculitis: These vasculitides classically involve small vessels, including capillaries, arterioles, and venules. They rarely cause irreversible dysfunction of vital organs and have better prognosis than systemic necrotizing vasculitides. Trigger is usually endogenous or exogenous antigen exposure. Cutaneous manifestations dominate the clinical picture but involvement of other organs and the peripheral nervous

system also is noted. The hypersensitivity vasculitides include the following:

Henoch-Schönlein purpura

Serum sickness

Infectious vasculitis (eg, HIV, hepatitis B)

Drug-induced vasculitis (eg, cocaine, heroin)

Neoplasm (eg, chronic lymphocytic leukemia)

Cryoglobulinemia

Behçet syndrome

Giant cell arteritides: These vasculitides classically involve large and medium-sized vessels. Giant cell formation with mononuclear cell infiltrates is seen frequently. Peripheral neuropathy is rare and is seen in less than 15% of patients with temporal arteritis. The giant cell arteritides include the following:

Temporal arteritis

Takayasu arteritis

Connective tissue disease: Patients with connective tissue disease can present with systemic necrotizing vasculitis or hypersensitivity vasculitis. Rheumatoid arteritis (RA) is the connective tissue disease that most often causes vasculitis. Vasculitis develops in 8-25% of patients with RA, usually 10-15 years after onset of RA. Overall, vasculitic neuropathy occurs in 40-50% of patients with systemic vasculitis. Systemic lupus

erythematous presents as polyneuropathy in 6-21% of patients. Connective tissue diseases most often associated with vasculitis include the following:

Rheumatoid arteritis

Systemic lupus erythematous

Sjögren syndrome

Systemic sclerosis

Nonsystemic vasculitic neuropathy

Localized vasculitis affects either the central nervous system (primary central nervous system angiitis) or the peripheral nervous system. Nonsystemic vasculitic neuropathy involves small and medium-sized arteries.

Clinical and histologic presentation is similar to that of neuropathy observed in systemic vasculitis but without any other organ involvement.

Nonsystemic vasculitic neuropathy represents one third of all vasculitic neuropathies. Prognosis is better than that of systemic vasculitic neuropathy.

Paraneoplastic vasculitic neuropathy: Paraneoplastic vasculitic neuropathy is a rare paraneoplastic syndrome characterized by nonsystemic subacute vasculitic neuropathy. The cancers most commonly associated with paraneoplastic vasculitic neuropathy are small cell lung cancer and lymphomas.

Laboratory Studies

Laboratory studies are more helpful in systemic than nonsystemic vasculitis; however, obtain the following studies in any patient in whom vasculitic neuropathy is suspected. In general, place the results in the context of the clinical presentation for a diagnosis. For those individuals with multiple high levels of the inflammatory markers listed here, consultation with a rheumatologist is strongly recommended.

Nonsystemic vasculitic neuropathy has a better prognosis than systemic vasculitic neuropathy. The former may have normal laboratory results, while systemic vasculitis often features elevated antinuclear antibody (ANA) titers, erythrocyte sedimentation rate (ESR), and other more specific markers of disease.

ESR (high, after age adjusted) - More than 70% of patients show ESR >20 mm/h

Antinuclear antibody titer (high in systemic diseases associated with vasculitic neuropathy)

Extractable nuclear antigens, p-ANCA and c-ANCA

Rheumatoid factor

Antineutrophil cytoplasmic antibodies

Hepatic enzymes

Renal function tests

Serum complement

Serum immunoelectrophoresis (or immunofixation) and quantitative immunoglobulins

Cryoglobulins

Hepatitis B antigen and antibody

Hepatitis C antigen

Routine cell count and serum electrolytes are indicated. Anemia is present in up to 30% of patients.

Serum analysis for other common causes of neuropathy, including hemoglobin A1c (HbA1c) and fasting glucose to rule out diabetes, thyroid function tests, B-12 and folate, and rapid plasma reagent (RPR).

CSF analysis can show high protein levels (>50 mg) in a small percentage of patients.

Imaging Studies

Brain imaging studies are usually not necessary, and a central nervous system etiology can be excluded comfortably by an accurate neurologic examination.

Magnetic resonance imaging (MRI) of the spine can be helpful in excluding a spinal nerve root lesion when suggested.

Other Tests

Nerve conduction studies and electromyography Electrodiagnostic testing is essential in making the diagnosis of any neuropathy, especially in vasculitic neuropathy. Electrodiagnostic testing can help accurately define the pathophysiology and localize the extent and distribution of the neuropathy. It also can provide information on whether the disease is active in the form of signs of active denervation, which accordingly facilitates choice of treatment protocol.

The predominant electrophysiologic feature of vasculitic mononeuropathy multiplex is axonal loss. "Conduction block" in vasculitic mononeuropathy multiplex is secondary to focal axonal conduction failure, presumably related to infarct of the axon.

Needle electromyography can demonstrate denervation potentials. Presence of positive sharp waves and fibrillation potentials indicates active denervation. Amplitude and duration of motor units assess the duration of axon loss and the presence of

reinnervation changes. Recruitment pattern identifies the amount of functional axonal loss.

Collins MP et al; [10] in a study titled Nonsystemic Vasculitic Neuropathy: Update on Diagnosis, Classification, Pathogenesis, and Treatment has said that the primary systemic vasculitides are autoimmune disorders characterized by chronic immune responses directed against vascular structures. They commonly affect small or medium-sized vessels in the peripheral nervous system (PNS), producing vasculitic neuropathies. Some patients develop vasculitis clinically restricted to the PNS, known as nonsystemic vasculitic neuropathy (NSVN), the most commonly encountered vasculitic neuropathy in pathologically based series. Diabetic and nondiabetic radiculoplexus neuropathies are clinical variants of NSVN. NSVN is clinically similar to systemic vasculitis-associated neuropathies except for reduced severity. Patients most commonly present with progressive, stepwise pain, weakness, and numbness over multiple months. Almost all exhibit a multifocal or asymmetric, distally accentuated pattern of involvement. The most commonly affected nerves are the common peroneal nerve in the leg and the ulnar nerve in the arm. Sedimentation rate is mildly to moderately elevated in 50%; other markers of systemic inflammation are generally normal. Electrodiagnostic studies reveal a predominantly axonal, asymmetric, sensorimotor polyneuropathy, but pseudo-conduction blocks may occur. Definite diagnosis requires biopsy evidence of vascular inflammation and signs of active or remote vascular damage. In biopsies lacking definite vasculitis, the diagnosis is suspected if axonal alterations are accompanied by

perivascular inflammation and such supportive features as Wallerian-like degeneration, asymmetric fiber loss, hemosiderin, vascular immune deposits, neovascularization, myofiber necrosis/regeneration, focal perineurial damage, and endoneurial purpura.

In Approach to vasculitic neuropathies, Lacomis D, et al;[11] says since vasculitic neuropathy is treatable and potentially debilitating, clinicians should develop an approach to neuropathy that increases the likelihood of uncovering existing systemic or nonsystemic vasculitis. The presence of a connective tissue disease, systemic vasculitis, asymmetric or non--length-dependent axonal polyneuropathy, or multiple axonal mononeuropathies should heighten suspicion, but vasculitic neuropathy can also present as a distal symmetric polyneuropathy with or without other organ involvement. Electrodiagnostic testing utilizing extensive nerve conductions may be helpful in identifying features suggestive of vasculitic neuropathy and in selecting an abnormal nerve and muscle for biopsy confirmation. An array of laboratory tests may lead to identification of a systemic disorder that is either characterized by or predisposes to vasculitic neuropathy.

Burns TM, et al;[12] reviewed the classification of vasculitis and the clinical features of vasculitic neuropathy. Vasculitic neuropathy usually presents with painful mononeuropathies or an asymmetric polyneuropathy of acute or subacute onset. Neurologists should categorize vasculitic neuropathy in terms of clinical features (eg, systemic or non systemic) and in terms of histopathology (eg, nerve large arteriole

vasculitis or nerve microvasculitis). Systemic vasculitis should be classified further into one of the primary and secondary forms.

Gorson KC[13] in an update on Vasculitic neuropathies has stated that the diagnosis of vasculitic neuropathy is straightforward in patients with an established diagnosis of systemic vasculitis and classic features of mononeuritis multiplex. Most patients have clinical features of a subacute, progressive, generalized but asymmetric, painful, sensorimotor polyneuropathy. Laboratory tests often indicate features of systemic inflammation, such as an elevated sedimentation rate or positive anti-neutrophil cytoplasmic antibody, and electrodiagnostic evaluation shows multiple mononeuropathies or a confluent, asymmetric axonal neuropathy. Nerve biopsy is necessary to establish the diagnosis in most cases, particularly in patients with NSVN.

Schweikert K et al;[14] in Contribution of nerve biopsy to unclassified neuropathy has determined the etiology of the neuropathies in 14 patients (37%), i.e. in 15% of chronic symmetric, 30% of chronic asymmetric, 50% of subacute symmetric and 62.5% of subacute asymmetric neuropathies. The biopsy was diagnostic in 6 patients (16%), where it showed a vasculitis, and supportive in 8 patients (21%). He concluded that contribution of nerve biopsy to the diagnosis of peripheral neuropathy was highest in acute and subacute asymmetric forms of neuropathy and lowest in chronic symmetric forms. The main indication for nerve biopsy remains the diagnosis of vasculitic neuropathy, a potentially treatable disorder.

Vital C et al;[15] reviewed 202 biopsies performed on patients with suspected vasculitic neuropathy, of which 24 Churg-Strauss cases are studied separately. Specimens from the superficial peroneal nerve and peroneus brevis muscle were taken simultaneously by one incision. Without taking into account constitutional signs, systemic involvement was present in 131 patients, whereas the remaining 47 corresponded to non-systemic patients with lesions limited to peripheral nervous system and adjoining muscles. Diagnosis of panarteritis nodosa or microscopic polyangiitis, according to the size of involved vessels, was attested by an infiltration of vessel walls by inflammatory cells associated with fibrinoid necrosis or sclerosis. Microvasculitis was diagnosed when inflammatory infiltration concerned small vessels with few or no smooth-muscle fibers and without any necrosis. Microvasculitis was present in 11 of 46 non-systemic cases, and this predominance is statistically significant. Isolated perivascular cell infiltrates in the epineurium were considered not significant but allowed the diagnosis of 'probable vasculitis' if associated with at least one of the following features: regenerating small vessels, endoneurial purpura, asymmetric nerve fiber loss, and/or asymmetric acute axonal degeneration. Necrotizing vasculitis was visible in 60 cases: in nerve (16 cases), in muscle (19 cases), and both (25 cases). Microvasculitis was present in 25 cases: in nerve (19 cases), muscle (four cases), or both (two cases). Moreover, granulomatous vasculitis was found in the nerve of one non-systemic patient presenting also sarcoid granulomas in muscle. There were 24 'probable vasculitis' and 68 negative cases. Muscle biopsy improved the yield of definite vasculitis

by 27%.

Collins MP, Periquet MI; [6] in a study on Isolated vasculitis of the peripheral nervous system has stated that Vasculitis restricted to the peripheral nervous system (PNS), referred to as nonsystemic vasculitic neuropathy (NSVN), has been described in many reports since 1985 but remains a poorly understood and perhaps under-recognized condition. There are no uniform diagnostic criteria. Classification is complicated by the occurrence of vasculitic neuropathies in many systemic vasculitides affecting small-to-medium-sized vessels and such clinical variants as nonsystemic skin/nerve vasculitis and diabetic/non-diabetic lumbosacral radiculoplexus neuropathy. Most patients present with painful, stepwise progressive, distal-predominant, asymmetric or multifocal, sensory-motor deficits evolving over months-to-years. NSVN is identical to but less severe than systemic vasculitis-associated neuropathies (SVNs). All vasculitic neuropathies are axonal by electrodiagnostic/pathologic criteria. Laboratory testing is unremarkable except for mildly elevated erythrocyte sedimentation rate (ESR) in 50%. Highly elevated ESRs, leukocytosis, rheumatoid factors, and anti-neutrophil cytoplasmic antibodies (ANCAs) raise concern for underlying systemic vasculitis. Without a specific clinical/laboratory marker, the condition depends on nerve biopsy for diagnosis. Biopsies showing necrotizing vasculitis are about 50% sensitive, mandating reliance on "suspicious" changes in many patients. Vasculitic lesions predominate in smaller epineurial vessels and are milder than those in SVNs. The disorder is often accompanied by subclinical involvement of adjacent muscles and skin. NSVN has the potential to

spontaneously relapse and remit but neurologic deficits accumulate. No randomized controlled trials have been performed, but one retrospective cohort survey showed combination therapy to be more effective than prednisone alone. Although most patients have a good outcome, more than 30% relapse and 60% have residual pain. Many nosologic, pathogenic, diagnostic, and therapeutic questions remain unanswered.

Collins MP, Periquet MI;[16] in Non-systemic vasculitic neuropathy reviewed the literature on non-systemic vasculitic neuropathy, with emphasis on recent advances, summarizing the clinical presentation, diagnosis, pathology, treatment, and outcome of this condition, and speculating on its nosological status vis-à-vis the systemic vasculitides. Analysis of the clinical characteristics of this cohort demonstrated a higher incidence of painful, asymmetric, overlapping deficits than in previous studies. Extended follow-up revealed a high relapse rate, low risk of systemic spread, high incidence of chronic pain, relatively good neurological outcome, and low mortality rate. Analysis of therapeutic responses showed better outcomes with combination therapy than corticosteroid monotherapy. Another recent report proposed a role for magnetic resonance angiography in the diagnosis and follow-up of non-systemic vasculitic neuropathy. Recent pathological studies implicated proinflammatory cytokines and matrix metalloproteinase-9 in the mediation of vascular and axonal damage in non-systemic vasculitic neuropathy. Non-systemic vasculitic neuropathy is one of many localized vasculitides, with involvement restricted to nerves and (possibly) muscles. Inclusion and exclusion criteria differ between reported cohorts. All require a nerve

biopsy diagnostic of or suspicious for vasculitis and no extra-neuromuscular involvement. Patients typically present subacutely with a painful, multifocal/asymmetric, distal-predominant neuropathy. In the absence of clinical or laboratory evidence of systemic vasculitis or a condition predisposing to such, prognosis with treatment is good. Pathological data are supportive of a primary T-cell-mediated immunopathogenesis. Some patients classified as having non-systemic vasculitic neuropathy have a systemic vasculitis presenting with neuropathy; in others, the disease is organ-specific.

Said G, Lacroix C.;[2] in a study on Primary and secondary vasculitic neuropathy reported that focal and multifocal neuropathy occur as a consequence of destruction of the arterial wall and occlusion of the lumen of small epineurial arteries. Vasculitis may also complicate the course of other conditions ranging from infection with the HIV and with the B and C hepatitis viruses to diabetes and sarcoidosis. Pathologically polymorphonuclear cells are present in the infiltrates of the vessel wall in primary necrotizing vasculitis, while in secondary vasculitis the inflammatory infiltrate is mainly composed of mononuclear cells. In all instances symptomatic vasculitis requires corticosteroid to control the inflammatory process and prevent further ischemic nerve lesions.

Pagnoux C, Guillevin L.;[17] in Peripheral neuropathy in systemic vasculitides has found that Vasculitic neuropathy may result from primary or secondary systemic

vasculitides, or may be restricted to the PNS, in a form that is now also considered to be a systemic vasculitis. The blood-nerve barrier is not as efficient as the blood-brain barrier. Inflammatory cell infiltration into the vasa nervorum and epineurial arteries leads to ischemic axonal nerve injury and is facilitated by additional breaches in the blood-nerve barrier, induced by proinflammatory cytokines, oxidative stress-derived molecules, and matrix metalloproteinases. Although animal models of myeloperoxidase or, now, proteinase 3-antineutrophil cytoplasmic autoantibody-inducing vasculitis have been developed, they do not support a role for antineutrophil cytoplasmic autoantibodies in PNS involvement. Treatment should be chosen based on the other organ involvement and the patient's general condition. When PNS involvement is isolated, corticosteroids alone should be used as first-line treatment. Apart from the so-called nonsystemic nerve vasculitis, PNS involvement is rarely the sole clinical sign of systemic necrotizing vasculitis, and its association with other typical manifestations is often suggestive of the diagnosis of vasculitis. Herein are summarized recent advances that have clarified but not yet fully elucidated the pathogenesis of peripheral neuropathy in systemic vasculitides, together with the latest clinical findings and therapeutic strategies.

Seo JH, Ryan HF, Claussen GC, Thomas TD, Oh SJ; [18] in Sensory neuropathy in vasculitis: a clinical, pathologic, and electrophysiologic study presented the clinical, pathologic, and electrophysiologic features of 17 (16%) cases of sensory neuropathy in vasculitis (SNV) among 106 cases with histologically proven vasculitic neuropathy that were collected over the last 30 years. In 41% of cases, SNV was found as systemic

vasculitic neuropathy in association with primary vasculitic disease. The most common clinical presentation was symmetric polyneuropathy, seen in 53% of cases. The most common nerve conduction pattern was diffuse neuropathy pattern of axonal degeneration. Sural nerve biopsy was diagnostic in 88% of cases. In two cases, muscle biopsy was necessary for the definite diagnosis of vasculitis. Non-systemic SNV is usually benign. Of 11 patients followed for longer than 2 years, none developed motor weakness due to neuropathy. Sensory neuropathy, regardless of symmetry, can be due to vasculitis.

Vrancken AF, Notermans NC, Jansen GH, Wokke JH, Said G; [19] in Progressive idiopathic axonal neuropathy--a comparative clinical and histopathological study with vasculitic neuropathy evaluated whether progressive idiopathic axonal neuropathy could be a pathologically difficult to prove vasculitic neuropathy pathologically difficult to prove or if it could be a separate clinical entity (i. e. with the axon as the primary immunological target), we performed a comparative clinical and histopathological study in 10 patients with progressive idiopathic axonal neuropathy, 10 patients with vasculitic neuropathy, and 12 patients with chronic idiopathic axonal polyneuropathy (CIAP). The clinical features and disease course in patients with progressive idiopathic axonal neuropathy and patients with vasculitic neuropathy were similar. Six patients with progressive idiopathic axonal neuropathy had been treated with prednisone and/or intravenous immunoglobulin. Disability decreased in all these six patients, but also in two of the four non-treated patients. Upon reviewing the sural nerve biopsy specimens,

vasculitis was found in one patient with progressive idiopathic axonal neuropathy. Vasculitis-associated signs of ischemic injury or inflammation (most notably: large variation in fascicular axonal degeneration, perivascular inflammation, inflammation of the blood vessel wall without lumen obstruction) were found in four patients with progressive idiopathic axonal neuropathy, in all patients with vasculitic neuropathy, but were absent in patients with CIAP. The findings show that there is a small chance of finding sural nerve vasculitis upon scrutinising biopsy examination in progressive idiopathic axonal neuropathy. The presence of vasculitis-associated signs in progressive idiopathic axonal neuropathy suggests that some of these patients could have vasculitic neuropathy, even if vasculitic lesions cannot be demonstrated. However, if inflammatory changes cannot be demonstrated this does not preclude an immune-mediated origin.

Carolei A, Sacco S; [20] in Central nervous system vasculitis states that vasculitis is an inflammation of the vessel wall. It may be either primary or secondary. Primary vasculitis includes systemic vasculitis (large, medium, and small-vessel vasculitis) and localized vasculitis (isolated angiitis of the central nervous system and non-systemic vasculitic neuropathy). Secondary vasculitis may be present in connective tissue disorders or may be caused by infections, neoplasms, and substance abuse. Patients presenting with symptoms suggestive of vasculitis require brain neuroimaging, lumbar puncture, and angiography, but only biopsy allows a definite diagnosis.

Heuss D, Schlotter-Weigel B, Sommer C;[21] in Diagnosis and therapy of vasculitic

neuropathy. Consensus statement of the German Centers for Neuromuscular Disease distinguished neuropathies associated with primary and secondary systemic vasculitis, with rheumatic diseases, with malignant disorders, drug-induced vasculitis and the non-systemic vasculitic neuropathies (NSVN). The typical clinical picture consists in an asymmetric or multifocal, painful sensorimotor neuropathy with an acute, subacute or chronic course and acute relapses. Neurophysiology reveals an active, asymmetric, axonal sensorimotor neuropathy. The disorders usually respond to immunosuppressive treatment. A diagnosis of definite vasculitis can be made with evidence of vasculitis in a biopsy specimen. The absence of positive morphological evidence, however, does not exclude the diagnosis. There is no single laboratory test that can prove or exclude vasculitis, in NSVN even an elaborate panel of blood tests can show normal findings. Systemic vasculitis has an incidence of 4/100,000 per year and, untreated, has a poor prognosis, which is greatly improved by the use of immunosuppressive treatment. The prognosis of NSVN is generally better, although many patients need long term immunosuppression. Current treatment recommendations for vasculitic neuropathies are presented.

Griffin JW; [22] in his study on Vasculitic neuropathies has stated that vasculitis typically affects the 50- to 400-micron vessels of the vasa nervorum, leading to randomly distributed ischemia along the course of the nerve. This, in turn, leads to a distinctive picture, multiple mononeuropathy, as a frequent but not invariant clinical consequence of vasculitis. The diagnosis of vasculitic neuropathy is usually made by

biopsy histologic confirmation. The response to treatment varies among different vasculitides; vasculitis restricted to the peripheral nervous system is often especially responsive.

Said G.;[23] in his study on Vasculitic neuropathy states that the pathogenesis of primary vasculitides, which are assumed to have an autoimmune pathogenesis, is not well understood. The endothelial cell adhesion molecules seem to play an active role, which varies according to the histopathologic stage of vascular lesions. The role of genetic factors also seems quite important, at least in an experimental model. The reliability of antineutrophil cytoplasmic antibodies testing in diagnosis and follow-up of patients with vasculitis is reviewed. The conclusion is that antineutrophil cytoplasmic antibodies status can be a very useful diagnostic adjunct to the evaluation of patients with suspected Wegener's granulomatosis, but is not a substitute for clinical expertise and histopathologic data during the course of providing patient care. The neurological manifestations of Churg-Strauss syndrome (a variant of polyarteritis nodosa) are very similar to those that occur in polyarteritis nodosa. A role for vasculitis has been confirmed in proximal diabetic neuropathy, which may pave the way for new therapeutic developments.

Olney RK;[24] in his study on Neuropathies associated with connective tissue disease reported that neuropathies are a common neurologic manifestation of diffuse connective tissue disease. Vasculitic neuropathy requires prompt diagnosis and

treatment to improve its outcome. It is commonly multifocal but may be confluent and symmetrical. Vasculitic neuropathy needs to be distinguished from the more common syndromes of compression neuropathy, which may also be multifocal, and nonvasculitic distal axonal polyneuropathy. Sensory neuronopathy is a distinctive syndrome unique to Sjögren's syndrome among the connective tissue diseases. Trigeminal sensory neuropathy may be the presenting feature of systemic sclerosis or may develop during the course of other connective tissue diseases. This article reviews the clinical and diagnostic features of neuropathies associated with the common diffuse connective tissue diseases.

Davies L.; [25] in his study on Vasculitic neuropathy stated that patients with vasculitic neuropathy may present with either mononeuritis multiplex, or a symmetrical or asymmetrical sensorimotor neuropathy. In those patients whose neuropathy is part of a systemic vasculitis the neuropathy can be expected to improve leaving only mild or moderate functional disability. Nevertheless, the long-term outlook for such patients is poor with a 5-year survival of around 50% with most excess deaths being due to vascular disease. The prognosis in non-systemic vasculitic neuropathy is almost certainly substantially better than this. Treatment of vasculitic neuropathy should be based on diagnosis by tissue biopsy, usually of nerve, and early use of aggressive immunosuppression.

Kissel JT, Mendell JR;[26] in a study on Vasculitic neuropathy states that peripheral

neuropathy is common in many vasculitic syndromes and may be the only manifestation of the underlying vasculitic disease. Although traditional teaching has been that a true multiple mononeuropathy is the classic clinical presentation of vasculitic neuropathy, an overlapping (or extensive) multiple mononeuropathy or a distal symmetric polyneuropathy is commonly encountered. Similarly, the leukocytoclastic reaction has traditionally been considered the primary mechanism of vessel injury in these diseases, although more recent evidence suggests that cellular-mediated mechanisms may be more important in peripheral nerve. In this review, new concepts concerning the clinical presentation, pathogenesis, diagnosis, and treatment of vasculitic neuropathy are discussed, particularly in relation to the syndrome of isolated peripheral nerve vasculitis.

Oh SJ;[27] in Diagnostic usefulness and limitations of the sural nerve biopsy reviews the diagnostic usefulness and limitations of this procedure. Based on 385 sural nerve biopsies, we found clinically helpful or relevant information in 45% of cases. In 24% of cases, specific diagnoses were obtained, among which vasculitic neuropathy was most common.

OBJECTIVE

1. To correlate the clinico-pathologic, and electrophysiologic features of 30 cases of vasculitic neuropathy

2. To determine whether combined nerve (usually the sural) and muscle (usually the vastus lateralis) biopsy improved diagnostic yield compared with nerve biopsy alone.

MATERIALS AND METHODS

The study group comprised of all patients admitted to the Dept. of Neurology Govt Stanley Hospital between Jan 2007-Dec 2008 with a clinical diagnosis of vasculitic neuropathy, confirmed histopathologically with nerve and muscle biopsies.

The nerve biopsies were taken from the sural nerve and muscle biopsy was taken taken from the vastus lateralis muscle.

The biopsy specimens were sent IN 2% CIDEX SOLUTION to Dept. of Neuropathology, NIMHANS, Bangalore for tissue processing and histpathologic examination

Pathological selection criteria

Nerve biopsies were classified as showing definite or probable vasculitis. Definite vasculitis was diagnosed if endoneurial or epineurial vessels showed evidence of vessel wall infarction in association with perivascular or transmural infiltration by inflammatory cells. Vessel wall infarction was diagnosed if there was evidence of destruction and disorganisation of the muscularis by fibrinoid necrosis, disruption of the endothelium or internal elastic lamina, thrombosis of the lumen or haemorrhage into the wall of the vessel. Probable vasculitis was diagnosed if there was transmural or perivascular inflammation not accompanied by vessel wall infarction.

In muscle biopsy specimens, similar diagnostic criteria for definite vasculitis were applied. Probable vasculitis was diagnosed where transmural inflammation was not accompanied by fibrinoid necrosis of the vessel wall or any of the other vascular changes described above as representing evidence of definite vasculitis. In muscle, transmural inflammation alone without the additional features which were applied to nerve biopsies were sufficient to diagnose probable vasculitis.

Clinical and electrophysiological data

Clinical features were studied to provide clinical and electrophysiological data for all patients meeting the pathological criteria for vasculitis. All patients were clinically suspected of having vasculitis. The pattern of neuropathy was determined by the findings on clinical examination. Nerve conduction studies and electromyography were performed, using standard techniques.

Patients with pathologically confirmed vasculitis were divided into SVN and NSVN groups. The criteria that were used to define cases as NSVN were as follows: (1) no evidence of involvement outside the peripheral nervous system (except striated muscle) and (2) no underlying causative agent (hepatitis B, hepatitis C, HIV, drug exposure, connective tissue disorder, malignancy). Patients with diabetes mellitus were not excluded. Systemic vasculitis was defined as in the Chapel Hill Consensus Conference. Constitutional symptoms such as fever and weight loss and serological tests such as antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA),

erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF) were not in themselves used to diagnose SVN unless independent clinical criteria for the diagnosis of a connective tissue disorder were present.

Statistics were performed using SigmaStat 3.5 software. Categorical variables were analysed using the 2, Fisher's exact test or McNemar's test where appropriate. The Mann–Whitney rank sum test was used to compare the duration of symptoms prior to biopsy in SVN and NSVN cohorts as the data were not normally distributed.

RESULTS

Clinical features

Thirty patients were identified on the basis of a pathologically confirmed diagnosis of vasculitis between Jan 2007 and Dec 2008. 58% had SVN and 42% NSVN. There was a female preponderance (women:men 19:11). Age range at the time of biopsy was 18–68 years (mean 47 (SD 13)). The clinical features were more severe in the older cohort. Duration of symptoms prior to biopsy ranged from 1 to 40 months (mean 15 (SD 23), median 6). Mean duration of symptoms prior to biopsy was shorter in the SVN than in the NSVN group (8.5 vs 23.5 months, respectively) but this difference was not statistically significant (Mann–Whitney rank sum test $p = 0.36$). The majority (87%) of neuropathies were painful on presentation and the most common presentation was with either an asymmetric sensorimotor neuropathy or mononeuritis multiplex (45% and 20% of patients, respectively). 17% had only sensory findings on presentation. There was a distal predominance. Electrophysiologically the most commonly involved nerve was the peroneal (86% of patients); in the upper limbs the most commonly involved nerve was the ulnar (63% of patients).

In the NSVN group, 16% of patients suffered weight loss and 5% had fever. As expected, systemic features were much commoner in the SVN group ($p<0.001$, comparing the proportion of patients with systemic symptoms SVN versus NSVN; Fisher's exact test), in which weight loss occurred in 52% and fever in 18%. In the SVN

group there were a number of additional features, including: fever(26%), arthralgia (23%), malaise(19%),

Laboratory findings

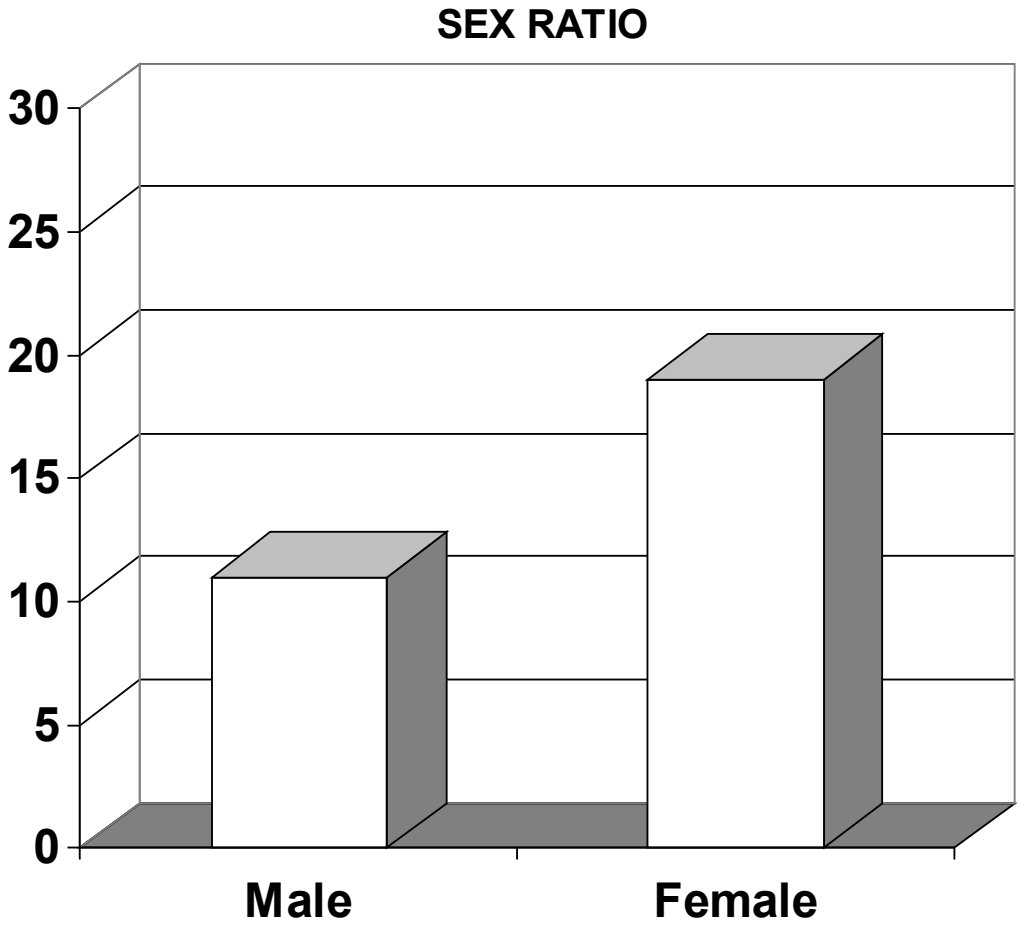
Patients with SVN compared with those with NSVN were significantly more anaemic ($p = 0.004$, Fisher's exact test) had a raised ESR ($p = 0.01$, 2 test) and had a positive serology for ANCA ($p = 0.003$, Fisher's exact test). A greater proportion of patients with SVN had positive ANA and RF serology compared with patients with NSVN but these differences did not reach significance.

Neurophysiology

The most frequent finding was that of an asymmetric or patchy axonal motor and sensory peripheral neuropathy (43%). Relatively infrequent mononeuropathies were identified (8%). Some patients were reported to have had a symmetrical or generalised neuropathy (25%). Occasional borderline motor slowing was identified but rarely in the frankly demyelinating range (less than 38 m/s in the upper limbs). In all cases of marked motor slowing there was evidence of significant or severe loss of motor axons. There were no cases with convincing findings of demyelination and no cases of partial motor conduction block. 17% of patients had a principally sensory neuropathy.

Pathological findings

In 36% of patients the nerve biopsy demonstrated definite and in 62% of patients probable vasculitis. In patients with SVN the nerve biopsy was more likely to show definite (as opposed to probable) vasculitis when compared with NSVN patients (48% vs 18%, $p = 0.04$, Fisher's exact test). The muscle biopsy demonstrated vasculitis in 48% of the vastus lateralis biopsies; 13% muscle biopsies showed definite and 35% probable vasculitis. None of the muscle biopsies demonstrating probable vasculitis had accompanying signs of remote vascular injury. Of those muscle biopsies which did not demonstrate vasculitis, five showed an inflammatory cell infiltrate. 21 % muscle biopsies showed myofibre necrosis and 63 % showed neurogenic changes.


SEX RATIO
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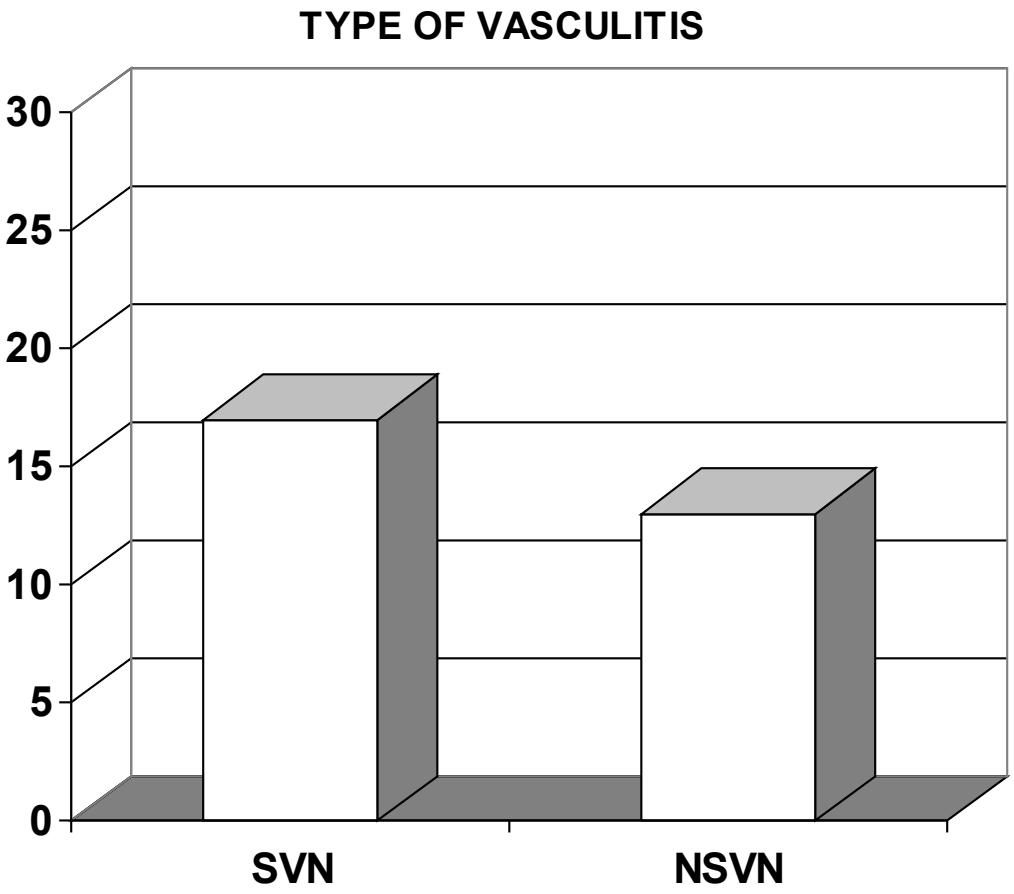
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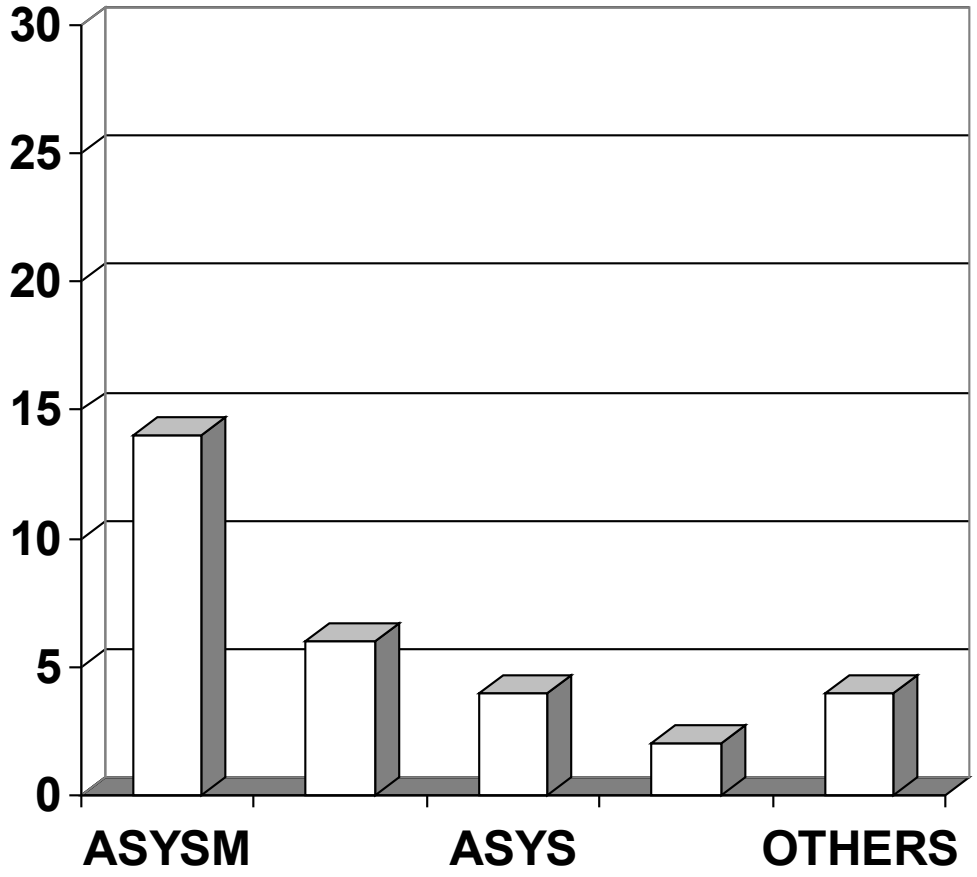
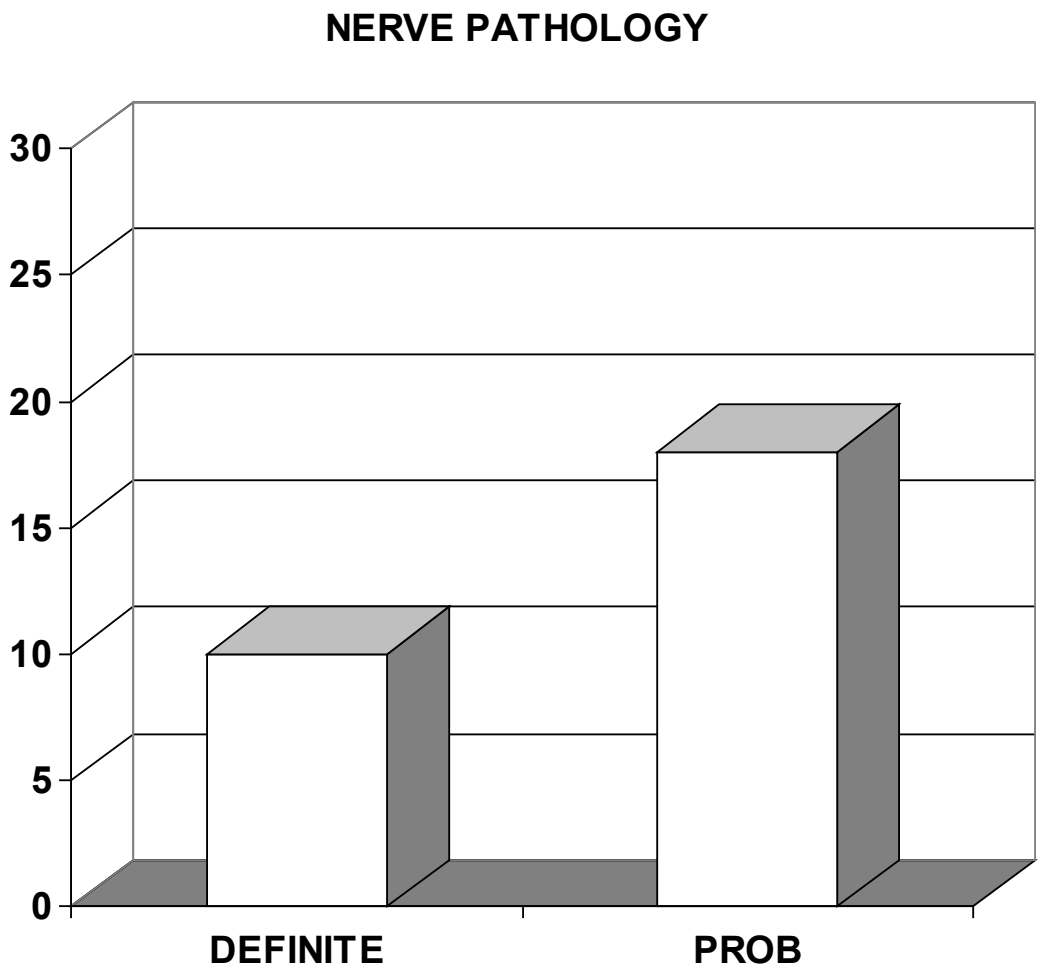
TYPE OF NEUROPATHY

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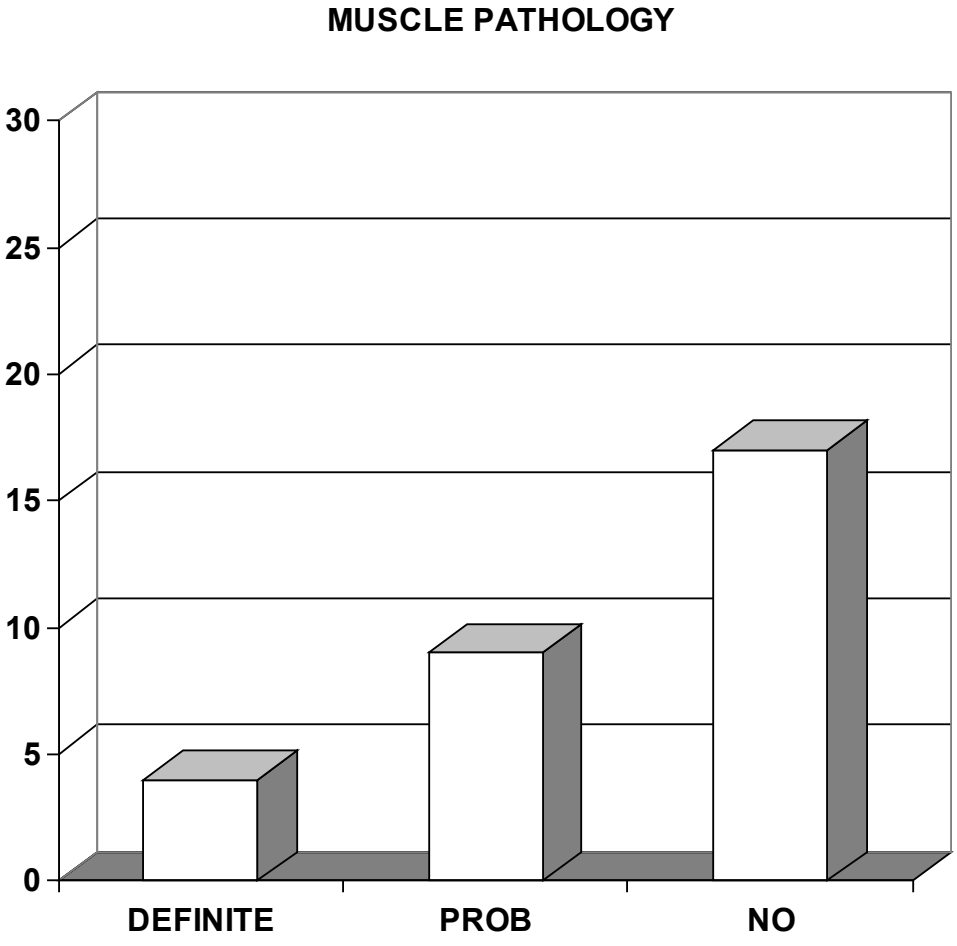
MUSCLE PATHOLOGY
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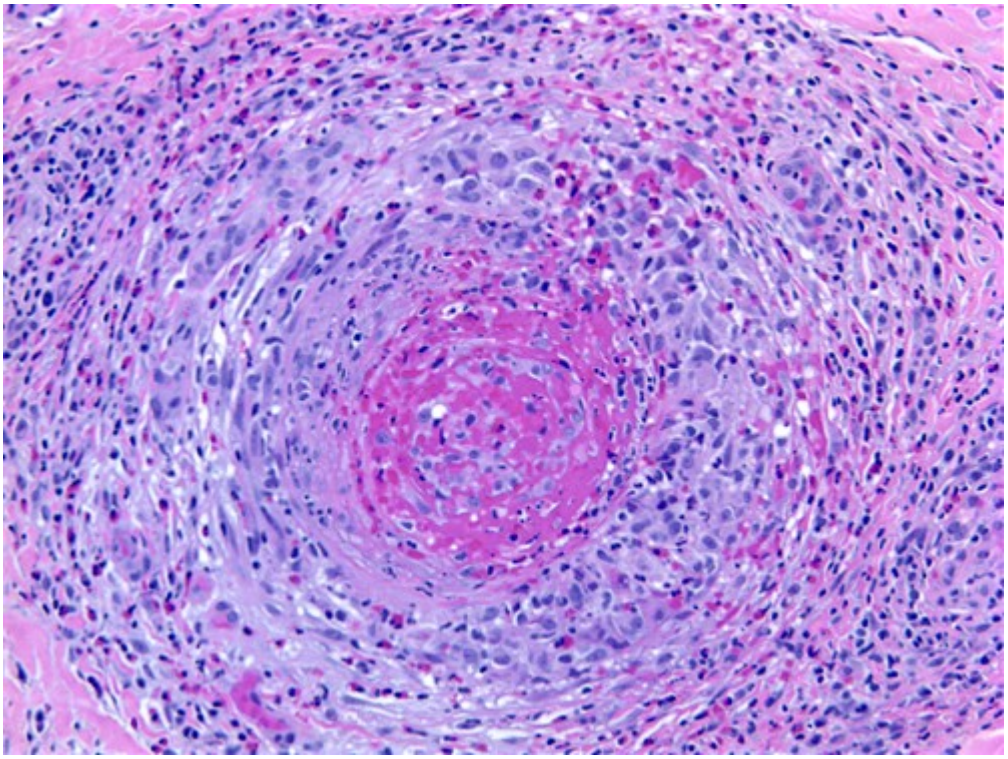
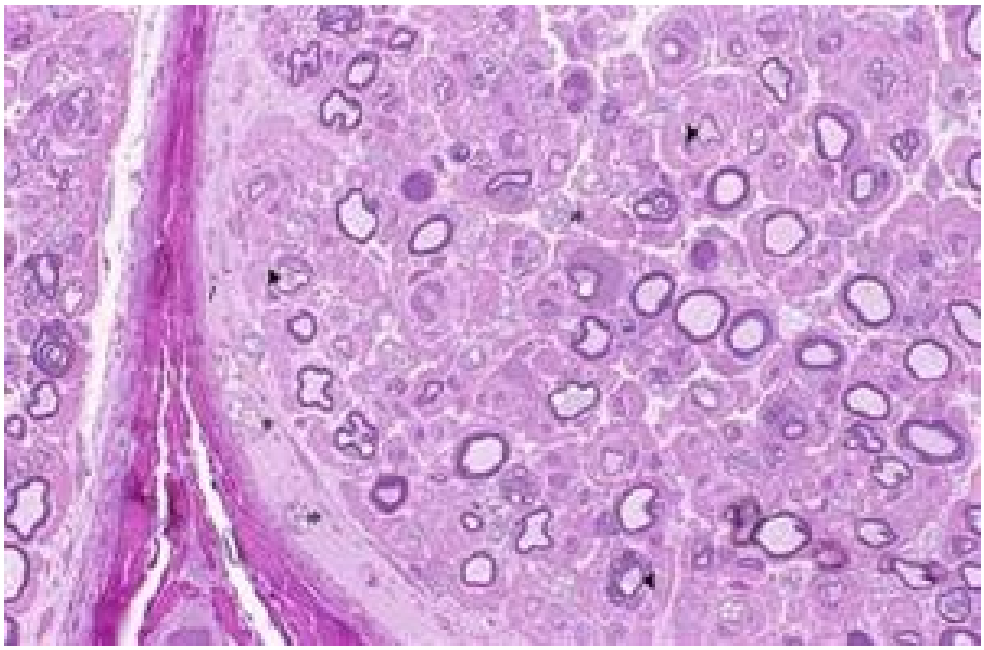
HISTOPATHOLOGICAL SLIDE PICTURES OF NERVE & MUSCLE BIOPSY

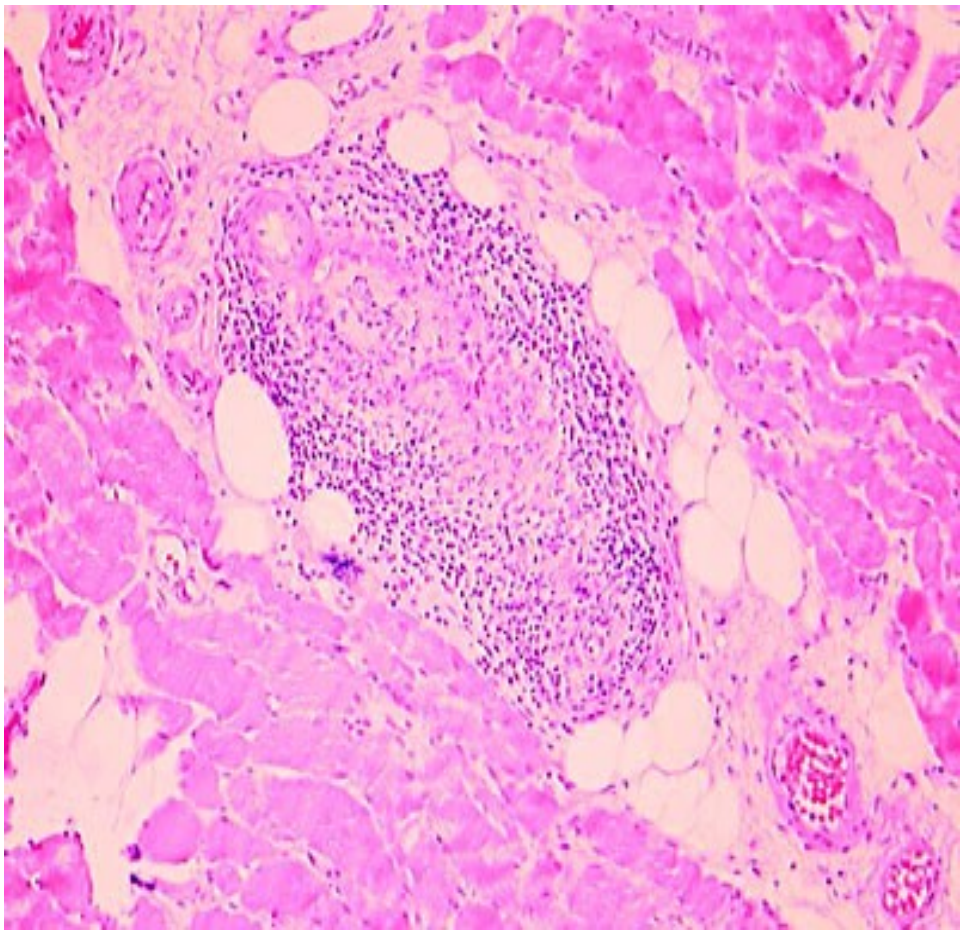


NERVE BIOPSY IN VASCULITIS

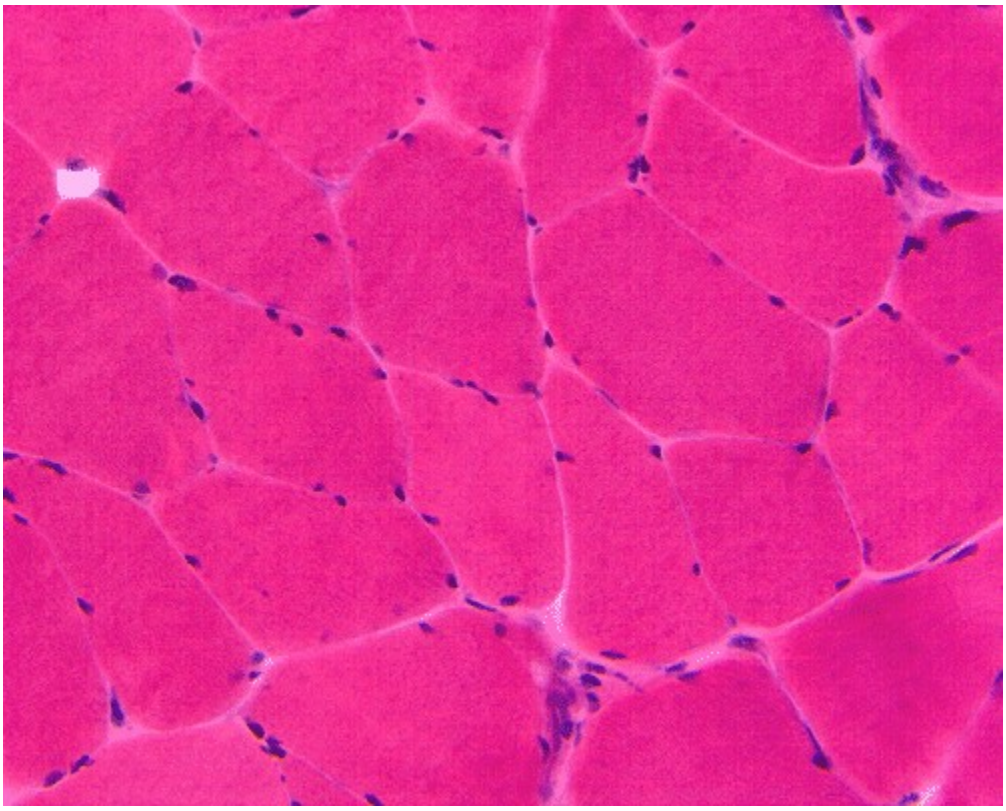


NERVE BIOPSY IN VASCULITIS

NERVE BIOPSY



MUSCLE BIOPSY IN VASCULITIS



MUSCLE BIOPSY IN VASCULITIS

DISCUSSION

The demographic features of our vasculitis cohort were similar to previous studies, showing a female predominance and a tendency for the condition to affect the

elderly.[5, 7, 11–14] In agreement with previous reports,[3 ,6, 7, 15, 16] we have found that pain is a prominent symptom described by the vast majority (87%) of our patients. Most of our patients presented with an asymmetric neuropathy, usually either an asymmetric sensorimotor neuropathy (45%) or mononeuritis multiplex (20%). Only 11% presented with a symmetrical sensorimotor neuropathy. Reports of the proportion of patients presenting with symmetrical compared with asymmetric findings in the literature vary greatly from 2% of patients having a symmetrical neuropathy in one recent study of NSVN[6] up to 76%[17] in a study involving patients with SVN and NSVN. These discrepancies may relate to the extent to which minor asymmetries on examination are taken into account, or to the different patient populations. No patient in our cohort had a purely motor neuropathy although 15% presented with a pure sensory neuropathy, a proportion similar to previous reports.[6, 7, 9, 12, 18,] The most commonly involved nerve in the lower limbs was the peroneal nerve and in the upper limbs the ulnar nerve. The frequent involvement of the peroneal nerve is compatible with experimental evidence demonstrating that the sciatic nerve bifurcation is a watershed zone, being particularly susceptible to ischaemia.[20]

Peripheral nerve vasculitis can occur either as part of a multisystem disorder (SVN) or as a disorder restricted to the peripheral nervous system (NSVN). In our cohort, patients with SVN had a shorter duration between symptom onset and nerve biopsy, and were more likely to have anaemia, raised inflammatory markers and positive serology for ANA, ANCA or RF than patients with NSVN.

It can be difficult to compare published cohorts of peripheral nerve vasculitis as different definitions of vasculitis have been used. In this study, we categorised peripheral nerve vasculitis into definite and probable. In definite vasculitis, there is evidence of both vascular inflammation as well as recent damage to the vessel wall. In probable vasculitis, there are transmural or perivascular inflammatory cells in combination with other features suggestive of vasculitis. A number of previous series have also subdivided cases into definite and probable vasculitis[6, 7] while some have been more restrictive by including only those cases in which there is evidence of both vessel wall inflammation and necrosis.[4] The inclusion of cases in which the nerve biopsy shows evidence of vessel wall inflammation without frank necrosis but with other features suspicious of vasculitis (ie, asymmetric nerve fibre loss, prominent Wallerian degeneration, predominant axonal changes) has been shown to increase the estimated sensitivity of the procedure from 61% to 86% with only a small loss of specificity.[12]

It was first reported in 1988 that combined nerve and muscle biopsy using superficial peroneal nerve (SPN) and peroneus brevis muscle (PBM) could increase the diagnostic yield compared with nerve biopsy alone. In a more recent review, the same authors described a larger cohort of 425 patients in which vasculitic lesions were found in muscle only in 28% of patients, nerve only in 45% and both in 31.5% of patients.[1] A number of other groups[9, 12, 21] describing combined SPN and PBM biopsy in the diagnosis of vasculitis have also found a sizeable percentage of patients in whom vasculitis is present in muscle but not nerve (varying between 9% and 27%). There are

fewer evaluations of diagnostic yield when combining sural nerve biopsy with vastus lateralis muscle biopsy. In 33 patients described as part of a cohort selected for the presence of muscle vasculitis (principally gastrocnemius), vasculitis was not found in the sural nerve in 20% of cases.[13] Claussen et al described a series of 115 combined sural nerve and muscle biopsies (principally tibialis anterior and gastrocnemius) performed for suspected vasculitis. Histopathological evidence of vasculitis was found in 39% of cases and in agreement with our own findings, combined muscle biopsy did not improve diagnostic yield (there were no cases where vasculitis was demonstrated in muscle but not in nerve).[22]

In contrast with a number of previous studies, we only found a small increase in diagnostic yield when performing combined nerve and muscle biopsy. Only one patient had evidence of probable vasculitis present in muscle but not in nerve.

There are potentially a number of reasons why we found only a small increase in the diagnostic yield from combined nerve and muscle biopsies in our study. In the vast majority of cases we have biopsied a proximal muscle (vastus lateralis) while most other groups have biopsied more distal muscles, such as either the PBM or gastrocnemius. There could be a distal predominance for muscle vasculitis. In our series, 46% of the muscle biopsies from patients with peripheral nerve vasculitis showed vasculitis. This is much lower than the figure of 80% using PBM described by Said and colleagues,[4] although two other groups have found results which vary between 31% and 59%.[9, 12] A

second possibility is the physical proximity of the SPN and PBM versus the remoteness of the sural nerve and vastus lateralis. It is possible that a contiguous muscle to an affected nerve is more likely to demonstrate vasculitis than a remote muscle, although this has not been studied. These differences may relate to the different nerves being biopsied. The sensitivity of SPN/PBM biopsy for vasculitis has been estimated at 60–70%[12, 18] and the sensitivity of sural nerve biopsy is given as 50%.[7, 23] However, it is difficult to draw conclusions given the different patient groups and definitions of vasculitis used in these studies. One study of NSVN patients did compare the sensitivity of SPN/PBM versus sural nerve biopsy in the diagnosis of definite vasculitis and found increased sensitivity of 58% versus 47%, respectively, but this was not statistically significant.[6] A recent study comparing complications following SPN/PBM versus sural nerve biopsy has shown that although SPN biopsy can lead to a greater area of sensory loss compared with sural nerve biopsy, there is very little difference in other complications.[24]

Differences in the published diagnostic yield of combined nerve and muscle biopsy may also relate to the case cohort (eg, the proportion of SVN versus NSVN cases) and the stringency of the criteria used to define vasculitis in peripheral nerve and muscle.

CONCLUSION

In our study there was a preponderence of females over males. The clinical features were more severe in older age group than younger age group. Asymmetric sensorimotor neuropathy was the most common clinical presentation. There were no casae of pure motor neuropathy. There was a preponderence of SVN over NSVN. In SVN there was a shorter duration between symptoms and nerve biopsy .The routine practice of performing of sural nerve and vasus lateralis biopsy does not significantly increase the diagnostic yield of vasculitic neuropathy.

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